The importance of red cell distribution width on gastric cancer: A preliminary study

Value of red cell distribution in gastric cancer

Dilek Erdem[1], Emre Erdem[2], Yasemin Turgut Kurt[3], Turgut Kacan[4], Bahiddin Yilmaz[5], Meral Gunaldi[6], Mahmut Buyuksimsek[7]

[1]Department of Medical Oncology, Bahcesehir University Medical School, Samsun Medical Park Hospital, Samsun,
[2]Department of Nephrology, Ondokuz Mayıs University Faculty of Medicine, Samsun,
[3]Department of Internal Medicine, Samsun Education and Research Hospital, Samsun,
[4]Department of Medical Oncology, Afyonkarahisar State Hospital, Afyon,
[5]Department of Medical Oncology, Ondokuz Mayıs University Medical School, Samsun,
[6]Department of Medical Oncology, Istanbul Aydin University VM Medical Park Hospital, Istanbul,
[7]Department of Medical Oncology, Cukurova University Medical School, Adana, Turkey

Abstract

Aim: Red cell distribution width (RDW) is an elevated marker in several cancers like breast, colon, prostate and pancreatic cancer at the time of diagnosis. Gastric cancer (GC) is the fifth most common cancer and also the third leading cause of cancer deaths. We aimed to determine whether RDW values diagnosis in GC. Material and Method: This retrospective study included gastric cancer patients. Median age was 42-year old and sex- matched healthy controls. Blood samples were retrospectively obtained from the computerized patient database before surgery or chemotherapy/radiotherapy. Results: RDW, neutrophil-lymphocyte ratio (NLR) and platelet- lymphocyte ratio(PLR) were significantly higher in GC patients when compared to healthy subjects (RDW: 44,9 vs 41,4 p<0.0001, NLR: 3,40 vs 1,90 p<0.0001, PLR: 245,9 vs 131,1 p=0.007). There was no statistically significant association between these markers (RDW, NLR, and PLR) and stage, histopathological subgroups and metastasis stage at the time of diagnosis. Discussion: Elevated RDW is a simple, cheap and readily available marker and may be useful in GC at the time of early diagnosis especially. Also, NLR and PLR can accompany RDW in the assessment of GC.

Keywords

Gastric Cancer; Red Cell Distribution Width; Neutrophil to Lymphocyte Ratio; Platelet to Lymphocyte ratio

Introduction

RDW is a component of complete blood count (CBC) reflecting erythrocyte anisocytosis which means the heterogeneity of erythrocyte volume [1]. Its main role was limited to the differential diagnosis in anemias in the past, but recent data show that elevated RDW is associated with a very wide spectrum of diseases leading mostly to inflammation but also oxidative stress and malnutrition [2,3]. Some inflammatory diseases are related to high levels of RDW such as inflammatory bowel disease, rheumatoid arthritis, hypertension, atherosclerosis, heart failure etc. [4,5]. Also, elevated RDW can predict mortality[6]. Malign tumors are known to trigger chronic inflammation which can also be an inducer for cancer itself [7]. Cancer-associated inflammation causes cellular and genomic damage by releasing a number of oxidative molecules and increase cancer risk that affects RDW [8]. In addition, some anti-inflammatory agents and antioxidants were shown to decrease the risk of cancer [9]. GC remains a major health problem worldwide and also it is the fifth most common cancer and the third leading cause of cancer deaths [10]. GC is a very heterogeneous disease that is due not only to tumor characteristics but also to host-related factors. Therefore the diagnosis is difficult in general [11]. With regard to these features of GC, we hypothesized that elevation of basic RDW related to cancer-induced chronic inflammation and nutritional status might be a biomarker and might be used in the early detection of GC. Also, there are factors leading to inflammation in peripheral blood count like NLR and PLR which may increase in several diseases including many cancer types [12-14]. Thus, we aimed to reveal the role of RDW in the diagnosis of GC and contribute this idea with examining NLR and PLR.

Material and Method

This is a retrospective study performed between November 2011 and May 2014 in which patients of Samsun Education and Research Hospital Medical Oncology Department were reviewed. The data were collected from hospital records and patient files of 68 patients with GC and 42 healthy controls were analyzed. The data were noted before surgery. The exclusion criteria involved cardiac disease, chronic obstructive lung disease, thromboembolism, chronic renal failure, hepatic disorders, hypertension, acute and chronic infections, stroke, hematologic disease, and other accompanying cancer. None of the patients were on anticoagulant therapy. The diagnosis of GC was made pathologically by endoscopic biopsy or surgically resected specimen. The cancer stage was determined in accordance with the TNM (tumor-node-metastasis) classification system (International Union against Cancer; UICC-7). Patients characteristics involved demographics, pathologic features, and hematological parameters. The healthy group involved the people with no known disease admitted to the internal medicine outpatient clinic for a check-up. The laboratory parameters were recorded at diagnosis and prior to the therapy, and collected from a computerized patient database. White blood cell count (WBC), neutrophil, lymphocyte, platelet count (PLT) and RDW were analyzed in the complete blood count using the same analyzer (Mindray BC6800). Standard tubes with constant amount of ethylenediaminetetraacetic acid were used. Our laboratory gives the standard deviation (SD) of RDW as femtolitre (fl). The normal range for RDW-SD was between 35.1-46.3 fl. Neutrophil counts were between 1.56-6.13 $(10^3/mm^3)$ and lymphocyte counts were between 1.3-3.6 $(10^3/mm^3)$. NLR and PLR were calculated by dividing neutrophil and

platelet count to lymphocyte count, respectively. The procedures followed were in accordance with the ethical standards and with the Helsinki Declaration of 1975, as revised in 2000. All people gave their informed consent prior to their inclusion in the study. The SPSS 19.0 software package was used for statistical analysis of the compiled dataset. The Kolmogorov-Smirnov test was used to determine the normality of data. Descriptive analyses for normally distributed variables were means and standard deviations and for abnormally distributed variables were medians with interquantile ranges. The Student's t- test or Mann-Whitney U test were used to compare groups, with the cChi-Square test used for categorical variables. A p-value of less than .05 was considered statistically significant.

Results

The study included 68 GC patients and age- and sex-matched 42 controls. Their features and hematologic results are shown in Table 1. The median age among patients and healthy controls were 59.1 ± 11.5 (35-83) years and 56.3 ± 6.4 (44-70) years, respectively. There were 54 male (79 %) and 14 female (21 %) patients in GC group while healthy subjects included 28 males (67 %) and 14 females (33 %). GC patients had higher RDW (p<0.0001), NLR (p<0.0001) and PLR when compared to healthy subjects at the time of the diagnosis (p=0.007; Table 1). There was no correlation between RDW and stage (Table 2) and metastatic state at the time of diagnosis (Table 3).

Discussion

In the present study, we found a significant relationship between GC and elevation of RDW, NLR and PLR values at the time of diagnosis.
Inflammation, anemia and oxidative stress are important factors for developing cancer. Elevated RDW is associated with oxidative stress, inflammation, and anemia [1,15]. Recent data show that the relation between RDW and age and mortality is supported by many studies [16]. And also most of inflamatory disease are related with high levels of RDW [4,5]. Although the exact mechanisms of how RDW levels are influenced by inflammation are unknown, four main causes step forward in this issue: impaired iron metabolism, decreased red blood cell (RBC) survival, erythropoetin response and the overproduction of selective cytokines such as CRP (C-reactive protein), tumor necrosis factor alpha and interleukin-6 [7]. Elevated RDW is as-

Table 1. Hematological parameters at the time of diagnosis

	Healthy subjects (n=42)	Patients (n=68)	p-value
WBC $(10^3/\mu L)$	6868±1595	7570±3421	0.149
Neutrophil $(10^3/\mu L)$	3986±1431	4791±2998	0.062
Lymphocyte $(10^3/\mu L)$	2710±2813	1827±1002	0.020
Hemoglobin (g/dl)	13.5±1.4	11.4±1.5	<0.0001
MCV (fL)	86.3±4.5	81.3±7.9	<0.0001
MPV (fL)	11.3±12.1	9.4±1.1	0.20
PDW	15.8±0.66	12.1±2.5	<0.0001
PLT $(10^3/\mu L)$	284±51.8	370±748	0.458
RDW (%)	41.4±3.1	44.9±5.1	<0.0001
NLR	1.90±1.35	3.40±2.79	<0.0001
PLR	131.1±46.7	245.9±333.4	0.007

NLR: Neutrophil - Lymphocyte Ratio; PLR: Platelet- Lymphocyte Ratio; WBC: White blood cell count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; PDW: Platelet distribution width; PLT: platelet; RDW: red cell distribution width

Table 2. Hematological parameters of early and advanced stage of gastric cancer during diagnosis

	Early stage (n=18)	Advanced stage (n=50)	p- value
WBC (10³/µL)	7047±2037	7759±3799	0.829
Neutrophil (10³/µL)	4253±1570	4984±3361	0.857
Lymphocyte (10³/µL)	1825±848	1828±1060	0.813
Hemoglobin (g/dl)	11.7±1.3	11.2±1.5	0.237
MCV (fL)	80.0±9.6	81.8±7.3	0.541
MPV (fL)	9.5±0.9	9.4±1.1	0.775
PDW	12.4±2.2	12.0±2.6	0.436
PLT (10³/µL)	292.8±98.6	398.6±871.9	0.672
RDW (%)	43.7±3.3	45.3±5.5	0.428
NLR	3.11±3.14	3.5±2.68	0.345
PLR	198.6±135.8	263±380	0.749

NLR: Neutrophil -Lymphocyte Ratio; PLR: Platelet- Lymphocyte Ratio; WBC: White blood cell count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; PDW: Platelet distribution width; PLT: platelet; RDW: red cell distribution width

Table 3. Patients with or without metastasis during diagnosis

	No metastasis (n=43)	Metastatic cancer (n=25)	p- value
WBC (10³/µL)	6920±2385	8689±4546	0.160
Neutrophil (10³/µL)	4121±1638	5942±4269	0.186
Lymphocyte (10³/µL)	1770±951	1924±1098	0.770
Hemoglobin (g/dL)	11.6±1.4	11±1.5	0.075
MCV (fL)	81.9±8.7	80.4±6.6	0.363
MPV (fL)	9.5±1.0	9.3±1.2	0.376
PDW	12.2±2.3	11.9±2.8	0.476
PLT (10³/µL)	281±93.2	524.6±1229.2	0.985
RDW (%)	45.3±5.3	44.1±4.7	0.500
NLR	3.15±2.76	3.82±2.85	0.227
PLR	216±182.8	297.5±497.4	0.726

NLR: Neutrophil- Lymphocyte Ratio; PLR: Platelet- Lymphocyte Ratio; WBC: White blood cell count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; PDW: Platelet distribution width; PLT: platelet; RDW: red cell distribution width

sociated mostly with inflammation, which is frequently found in patients with cancer, that may trigger RDW change [6]. A study which included breast cancer patients showed higher RDW values and accepted it as a prognostic indicator, particularly in triple negative subtype where cancer-related inflammation may play a greater role in disease progression [13]. In another study, nutritional anemia was the cause of RDW elevation in colon cancer during diagnosis [16]. RDW in prostate cancer [17], pancreatic cancer [18], lung cancer [19] and kidney cancer [20] were studied but RDW-GC relation is extremely rare.

Several studies have shown a relation between GC and chronic inflammation until now [21]. There is still no appropriate blood test to show differentiation between GC and healthy subjects at the time of the diagnosis. NLR and PLR are two main inflammation markers studied in many cancer types and several studies revealed high NLR and PLR levels predicting inflammation in GC patients [22-24]; otherwise, with respect to other cancer types, there are only two studies on the relation of RDW to GC. In one of the studies, non-hematological cancers and bone marrow content were investigated and included only 5 GC patients [25]. The second study was about red blood cell parameters and venous thromboembolism risk in cancer and found a weak relation which is so far from the main idea of our study [20]. Therefore our study is the first to investigate relation between RDW and GC with both most crowded patient population and comparison between cancer and healthy subjects. We showed that RDW, NLR, and PLR are featured markers at the time of GC diagnosis. Basic RDW values were higher in GC which may be due to anemia and mainly chronic inflammation like colon cancer. RDW elevation due to oxidative stress may develop from many conditions causing chronic inflammation such as cancer [1,15]. Thus we may consume that RDW is an early indicator of oxidative stress and inflammation. Also, NLR and PLR, the inflammatory markers were higher in GC patients which may be attributed to cancer and its triggering inflammation. Despite other studies [18], in our study, there was no correlation between RDW and stage and metastatic state at the time of diagnosis. Therefore, we can't be able to decide whether the disease is at the later stage in the state of high RDW during diagnosis. There are some limitations in our study. Firstly, data reflected only a single center which may differ according to the population. Secondly, the study included retrospective analyses.

Thirdly, we did not follow the change of RDW during the course of disease and lastly, the correlation between RDW and other inflammatory markers such as CRP were not studied because CRP is not a routine test for a GC patient.

Conclusion
Elevated RDW is seen to estimate as a good marker at the diagnosis of GC. High levels of NLR and PLR accompany with a high level of RDW. This state explains RDW's inflammatory role in GC with this preliminary trial. These triplet markers can be strong diagnostic factors in GC when CBC is done routinely in future.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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